Evaluation of the Trial to Assess Chelation Therapy (TACT)

The Scientific Process, Peer Review, and Editorial Scrutiny

Howard Bauchner, MD
Phil B. Fontanarosa, MD, MBA
Robert M. Golub, MD

In this issue of *JAMA*, Lamas and colleagues[1] report the results of the Trial to Assess Chelation Therapy (TACT). In this multicenter clinical trial, 1708 patients with previous myocardial infarction (MI) were randomized to receive 40 infusions of chelation solution vs placebo. After a median follow-up of 55 months, the primary end point (a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina) occurred in 222 patients (26%) in the chelation group and in 261 patients (30%) in the placebo group, with the major between-group difference involving fewer coronary revascularization procedures in the chelation group (15%) than in the placebo group (18%). The authors conclude that although chelation therapy modestly reduced the risk of a composite of adverse cardiovascular outcomes, the results "are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI."

This 10-year, $31 million, National Institutes of Health (NIH)–funded study conducted under the auspices of the National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine was intended to provide a rigorous evaluation of the use of chelation therapy, thereby providing evidence to inform patients who may be seeking an as yet unproven therapy for prevention and treatment of coronary artery disease. However, the study has generated controversy since its inception, with concerns that have included ethical issues involving an investigation by the Office for Human Research Protections (OHRP) regarding allegations of noncompliance with federal regulations for the protection of research participants[2]; study conduct issues involving allegations about the research capabilities and professional credentials of some study sites and site investigators,[2] as well as temporary suspension of trial enrollment; and fundamental scientific issues, involving concerns ranging from the safety of the chelating agent being studied to modification of the prespecified sample size and alteration of the prespecified statistical significance levels because of multiple interim analyses.

In light of these and other concerns, the editorial assessment of TACT, like other studies with complex interrelated issues, was extensive and comprehensive because the evaluation extends beyond assessment of scientific validity and clinical relevance. Accordingly, the editorial review and scientific assessment involved not only *JAMA*'s usual level of scrutiny and diligence in evaluating the research report, including careful review of the study protocols, statistical analysis plans, and methods papers—it also involved assessment of OHRP reports, other documents related to the ethical and regulatory aspects of trial conduct, and reports of professional and public reaction about the study.

In addition, the manuscript was extensively reviewed by independent peer reviewers with expertise in vascular medicine, study design, and statistical analysis; by several members of the *JAMA* editorial board; and by the *JAMA* cardiology contributing editors and senior editorial staff. The authors' revisions to the manuscript and their responses to the extensive critiques and concerns raised by this assessment were scholarly and thorough and directly addressed the issues and concerns, as evident in their extensive explanations about the statistical analysis (included in the online supplement with the article) and their forthright explanations and responses related to the editors' concerns about study ethics and trial conduct (included in the eAppendix to this Editorial at http://www.jama.com). As with all manuscripts, the final decision to publish the TACT report was made by the Editor in Chief and Executive Editor in consultation with the senior editorial staff.

Because articles published in journals like *JAMA* can influence the practice of medicine, this level of scrutiny of TACT reflects our commitment to fulfilling the responsibility to try to ensure that every article published in *JAMA* is valid and is reported accurately. This includes conducting a detailed methodological evaluation, presenting scientific information objectively and clearly, and making certain that study inferences and interpretations are communicated appropriately. Although peer review and editorial evaluation are not perfect for guaranteeing validity, these approaches provide for expert review, scientific assessment,

See also pp 1241 and 1293.

Author Affiliations: Dr Bauchner (howard.bauchner@jamanetwork.org) is Editor in Chief, Dr Fontanarosa is Executive Editor, and Dr Golub is Deputy Editor, *JAMA*.

and substantive revision to enhance the quality and presentation of scientific information.

Moreover, we recognize that publication of research reports in influential journals can do harm. For instance, the debacle involving the study reporting an association between the measles-mumps-rubella vaccine and autism[3] and the adverse effects that article had on immunization rates is an important reminder for all medical journal editors about the influence of their work on the attitudes, behaviors, and decisions of physicians and the nonphysician public.

Despite the limitations of the trial by Lamas et al and the continuing controversy surrounding TACT,[4] once the scientific issues had been addressed satisfactorily, the decision to publish this report in *JAMA* involved consideration of several important factors. First, this NIH-sponsored study had been approved by institutional review boards at 2 academic medical centers, was conducted in compliance with federal regulations, and the OHRP investigation had determined that the corrective actions that had been taken were such that patient protection was not at risk.

Second, despite numerous setbacks, criticisms, and concerns, the funding agencies and the investigators (who include one of the preeminent cardiovascular researchers and one of the most respected statisticians) demonstrated courage and persistence in continuing this trial to its completion.

Third, the study findings may provide novel hypotheses that merit further evaluation to help understand the pathophysiology of secondary prevention of vascular disease. Whether chelation of heavy metal ions or administration of high levels of antioxidants in chelation solutions have beneficial effects on vascular biology in established coronary disease remains to be determined.

Fourth, presentation of the study findings will enable cardiologists, other physicians, patients, and practitioners who provide chelation therapy to recognize that the possible benefit of chelation therapy, if there is any, is small, and to understand the important study limitations as discussed in the editorial by Nissen[5] (such as marginal statistical significance of the main findings, relatively high dropout rates, and the potential for unmasking). This evidence and information should serve to dissuade responsible practitioners from providing or recommending chelation therapy for patients with coronary disease and should discourage patients with previous MI from seeking this therapy with the hope of preventing subsequent cardiovascular events.

Fifth, although many physicians may have biases about the possible benefits of chelation therapy and other complementary and alternative therapies, the scientific process should prevail in providing evidence about these therapies. Reports of rigorous investigations should not be censored because of preexisting ideological positions.

Sixth, and perhaps most important, publication of the data from TACT will acknowledge the contributions of the 1708 patients who participated in this trial and who underwent multiple intravenous chelation infusions.

Clinical decision making is complex, reflecting a synthesis of evidence, physician experience, and patient preference, bound together by societal norms. As such, very few studies should immediately change clinical practice but, rather, most add incremental knowledge to the complex puzzle of a clinical decision. However, based on full consideration of the strengths and limitations of TACT, the conclusion is clear and should influence practice—these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease. Whether chelation therapy may have any role in the prevention and treatment of cardiovascular disease remains to be determined.

Online-Only Material: The eAppendix is available at http://www.jama.com.

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